ORIGINAL ARTICLE

The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection

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Background: Childhood urinary tract infection (UTI) with or without vesicoureteric reflux (VUR) may predispose to renal scarring. There is no clear consensus in the literature regarding imaging following UTI in infancy.

Aims: To define the role of cystography following a first UTI in children aged under 1 year, when urinary tract ultrasonography (US) is normal.

Methods: Retrospective data collection of 108 children (216 renal units) aged under 1 year at the time of a bacteriologically proven UTI. All had a normal US and underwent both catheter cystogram and DMSA test. Sensitivity, specificity, likelihood ratios positive and negative, and diagnostic odds ratio were calculated for VUR on cystography versus scarring on DMSA.

Results: VUR was shown in 25 (11.6%) renal units. Scarring on DMSA was seen in 8 (3.7 %) kidneys. Only 16% of kidneys with VUR had associated scarring; 50% of scarred kidneys were not associated with VUR. The likelihood ratio positive was 4.95 (95% CI 2.22 to 11.05) and the likelihood ratio negative was 0.56 (95% CI 0.28 to 1.11). The diagnostic odds ratio was 8.9, suggesting that cystography provided little additional information.

Conclusion: Since only 16% of children with VUR had an abnormal kidney, the presence of VUR does not identify a susceptible population with an abnormal kidney on DMSA. In the context of a normal ultrasound examination, cystography contributes little to the management of children under the age of 1 year with a UTI. In this context, a normal DMSA study reinforces the redundancy of cystography.

Urinary tract infection (UTI) in children may result in renal scarring. The belief that renal scarring predisposes to hypertension, chronic renal failure in early adulthood, and eclampsia in pregnancy, has been a major driving force in the impetus to investigate the first UTI. Doubt has recently been cast on the importance of renal scars in patients who develop any of the above diseases.[1–4] The important reason to investigate children with a UTI is to detect or exclude any renal or urinary tract abnormality that may be correctable, or predispose to repeated infections and long term renal damage. The commonest abnormality detected is invariably vesicoureteric reflux (VUR). The prevalence of VUR in children with UTI varies from 7% to 85% according to the review carried out by the American Academy of Pediatrics.[5]

There has been debate for many years over the role of VUR in children who develop renal scars following UTI. Two recent systematic reviews question the relation between VUR and renal scarring in children with UTI.[6 7]

Guidelines from the Royal College of Physicians of London (1991) recommend urinary tract ultrasonography (US) and cystography followed by renal 99m-technetium DMSA scan (DMSA) in the investigation of children presenting with a first UTI before their first birthday.[8] Guidelines of the American Academy of Pediatrics (1999) also recommend urinary tract ultrasonography (US) and cystography and do not define a clear role for DMSA scanning in this patient population.[9] A recent prospective study suggested that cystography, rather than US or DMSA should be the first-line investigation in first UTI in those under 2 years old, in a primary care population.[10] Another recent publication suggests that in the presence of a normal US and DMSA, no cystogram is necessary.[11]

There is clearly much confusion about the role of imaging in the investigation of a first UTI. We embarked on this study to answer the question, ''Does a child who presents with a first UTI before the age of 1 year, and who has a normal US, benefit from cystography?''.

METHODS

Our study involved two hospitals: a teaching hospital with a paediatric accident and emergency department (A&E) and a specialist paediatric hospital.

Patients

Entry criteria for this study were a bacteriological proven UTI in children under 1 year of age (at the time of the UTI), with a normal ultrasound examination, who had undergone both a catheter cystogram (a micturating cystourethrogram (MCUG) in boys and a direct isotope cystogram (DIC) in girls) and a DMSA scan. The original reports of urine microbiology, US, DMSA, and cystography were reviewed. During the four year period from January 2000 to December 2003, 218 children who had a DMSA scan for presumed UTI were identified; 108 children then fulfilled all the above criteria. The children underwent cystography six weeks after the acute infection, followed 3–6 months later by a DMSA scan.

Definitions used

Urine specimens containing at least 100 000 colony forming organisms/ml of a single bacterial pathogen were considered

Abbreviations: DIC, direct isotope cystogram; MCUG, micturating cystourethrogram; US, ultrasonography; UTI, urinary tract infection; VUR, vesicoureteric reflux

positive for a UTI. The ultrasound examination was considered normal if the report described normal kidneys bilaterally, with neither collecting system dilatation, nor dilatation of distal ureters, nor a renal pelvis exceeding 10 mm in transverse antero-posterior diameter (APRPD) and minimal or absent calyceal dilatation. (Kidneys with minimal calyceal splitting and APRPD <10 mm were included in the analysis.)

The acquisition of DMSA images was carried out 2–4 hours after the intravenous injection of tracer. A high resolution collimator, which provided magnification, was used. Posterior (for an acquisition of 250 K counts) and left and right posterior oblique views (for an acquisition of 200–350K counts) were obtained. No SPECT was used. A normal DMSA result was defined as a kidney with a differential function ⩾45%, and with no focal areas of reduced cortical tracer uptake.

VUR detected on MCUG was graded according to the international reflux grading system (1 to 5); all VUR on DIC was graded as 2/3 for the purpose of this study.

Statistical analysis

A 2×2 table comparing normal and abnormal DMSA results versus normal and abnormal cystogram results was constructed. Sensitivity, specificity, and likelihood ratios positive and negative were calculated for cystography, along with 95% confidence intervals, using DMSA as the gold standard. The diagnostic odds ratio was calculated as likelihood ratio positive divided by likelihood ratio negative.

Follow up

Reports of follow up imaging (1–4 years after the original UTI) were accessed via the radiology computer system.

RESULTS

A total of 108 children (55 girls and 53 boys), consisting of 216 renal units (kidney and ureter), met all the inclusion criteria. Age range was 0 months to 12 months, with a mean of 5.6 months (standard deviation 3.5 months) and a median of 5 months.

VUR was shown in 25 (11.6%) renal units (table 1). Twenty three renal units had grade 1–3 VUR, and two renal units had grade 4–5 VUR; these two were in a single boy who underwent MCUG. No cases of posterior urethral valves nor other urethral pathology were discovered in the boys studied.

DMSA abnormalities were seen in eight (3.7%) kidneys (table 1).

Three of the 23 renal units (13%) with grade 1–3 VUR and one of the two renal units (50%) with grade 4–5 VUR had DMSA abnormalities. Fifty per cent of ''scarred'' kidneys did not have associated VUR. The likelihood ratio positive was 4.95 and the likelihood ratio negative was 0.56. The sensitivity and specificity as well as likelihood ratios positive and negative for cystography using DMSA as the reference method are shown in table 2. The calculated diagnostic odds ratio was 8.90.

Follow up imaging was only done in six of the 21 kidneys which originally showed VUR, but had a normal DMSA scan 3–6 months after the first UTI.

Indirect isotope cystography, 3–4 years after the original studies showed resolution of the VUR in two of the originally refluxing kidneys. Normal ultrasound studies were documented in three other kidneys, a year after the original UTI. Only one of the six kidneys showed a possible small scar on ultrasound, but no DMSA confirmation of this was available. Hence five of the six kidneys followed up were normal.

DISCUSSION

A recent prospective multicentre study suggested that in children under 2 years of age with a febrile UTI, ultrasonography was not required, and the authors recommended an MCUG as the first imaging test.[10] This study stimulated active correspondence in which a view was expressed that the results presented did not support the conclusions drawn. We therefore undertook this retrospective analysis to ascertain if the data from a large teaching hospital with a primary referral pattern would substantiate the recommendations of Hoberman and colleagues.[10]

Cystography

At our institutions, the current practice is for all boys aged under 1 year, presenting with a UTI, to have an MCUG, in order to detect or exclude obstructive urethral pathology and VUR. Admittedly, significant obstructive urethral pathology in boys is likely to be picked up either on antenatal screening or on clinical presentation with renal impairment; however, this institution still has boys under 1 year of age referred with a first time UTI, who have posterior urethral valves.

Obstructive urethral pathology is very unlikely in girls, who therefore have a DIC, which, depending on technique, has a lower radiation burden than an MCUG. We accept that DIC does not show grade 1 VUR, but this is probably unimportant. Grading all reflux in girls as grade 2/3 may underestimate the incidence of grade 4 reflux, but this does not appear to change the outcome of this study.

Only a single one of the boys studied exhibited grade 4 VUR. This is probably because all our subjects were normal at ultrasonography, and higher grades of VUR are more likely to be associated with an abnormal ultrasound examination.

As serendipitously, similar numbers of girls (55) and boys (53) were studied, it is unlikely that the result was biased by any difference in sensitivity of DIC relative to MCUG in the detection of VUR.

DMSA in the detection of renal scarring

Although recent work proposes magnetic resonance imaging as a viable alternative, DMSA remains the ''gold standard'' for the detection of renal scarring.[12 13] Standardisation of criteria for the interpretation of DMSA scans results in high levels of intra- and inter-observer consistency.[14] SPECT has not been shown to have any advantages over planar DMSA

Table 1 Analysis of DMSA and cystogram findings (for kidneys)

	DMSA		
Cystogram	Abnormal	Normal	Total
Abnormal (VUR detected)	4	21	25
Normal	4	187	191
Total	8	208	216

Table 2 Comparison of cystogram findings (positive or negative for VUR) with DMSA findings (the gold standard: positive or negative for renal scarring)

		95% CI
Sensitivity	50%	21.5% to 78.5%
Specificity	89.9%	85.1% to 93.3%
Likelihood ratio +ve	4.95	2.22 to 11.05
Likelihood ratio −ve	0.56	0.27 to 1.11
Diagnostic odds ratio	8.9	2.07 to 38.25

for the detection of renal scars in everyday practice, and is therefore not routinely used in our department.[15 16]

As all kidneys included in the data analysis were, by definition, normal on US, with a maximum APRPD of 10 mm and minimal or absent calyceal dilatation, it is improbable that accumulation of tracer in a dilated renal collecting system could have contributed to an abnormal DMSA result.

Relatively few kidneys in our population were abnormal on DMSA scan, 3–6 months after the acute UTI. It is possible that prompt and appropriate antibiotic treatment during the acute illness prevented the development of renal scarring.

Correlation of scarring on DMSA with VUR on cystography

Our study showed that 84% (21/25) of kidneys with VUR did not have renal damage on DMSA and that 16% (4/25) had renal damage. The likelihood ratio positive was 4.95 and the likelihood ratio negative was 0.56. A likelihood ratio positive between 2 and 5 ''generates a small (but sometimes important) change in probability'' and one between 5 and 10 ''generates moderate shifts in pre-test to post-test probability.[17] A likelihood ratio negative between 0.5 and 1.0 ''alters the probability to a small (and rarely important) degree''.[17] The diagnostic odds ratio ''provides a robust measure for dichotomous results and test results''.[18] Useful tests tend to have diagnostic odds ratios well above 20.[18] Hence our results show that cystography, with a diagnostic odds ratio of 8.9, provides little additional useful information.

We analysed 216 kidneys in 108 patients. The majority of these were normal on both DMSA and cystography. As the number of ''abnormals'' was small, the stated 95% confidence intervals are wide. We have, however, studied a larger number of kidneys than any single study included in the recent systematic review by Gordon and colleagues.[7]

This was a retrospective study, dealing with actual clinical situations, and there was no clinical justification for performing follow up investigations in children who did not re-present with subsequent clinical problems. Hence follow up investigations were only carried out in six of 21 of the kidneys which originally showed VUR but had normal DMSA studies; five of these six kidneys had no abnormality on follow up. At the present time, clinicians at our institutions prescribe prophylactic antibiotics only in those children with VUR following a first UTI, until they are toilet trained.

In their prospective study, Hitzel and colleagues[11] calculated that VUR on MCUG had a positive predictive value of 32% and a negative predictive value of 69% for scarring when compared with DMSA (6 months post-UTI). The study of Hoberman *et al* showed similar results with only 15% of children with VUR having renal damage.[10] Systematic reviews by Wheeler and colleagues[6] and Gordon and colleagues,[7] looking at a total of 1396 children of all ages, concluded that VUR is a poor predictor of renal scarring. The latter systematic review was limited to children who had been hospitalised, based on the assumption that these were the sickest children with a UTI.[7] The present study, on the other hand, has not had made any assumptions about the degree of illness of the children, yet the findings are very similar.

In this study, an abnormal kidney on DMSA scan was only associated with VUR in 50% of cases, and 50% did not show VUR. Severe VUR (grades 3 or greater) may be associated with an increased incidence of renal damage, as was seen in this study; however, the question posed is ''When should cystography be undertaken in a young child with a proven UTI?'', If it is recommended that all young children with a proven UTI require a cystogram, then VUR will be detected in many children who have a normal kidney. Do these children warrant active prophylaxis? The answer to this question is far from clear, as there is no study showing the long term outcome of kidneys in this group. The international reflux study did not have an arm where the children who did not undergo surgery were followed up with no prophylaxis.[19] If the cystogram result were to dictate either the therapeutic regime and/or further imaging tests, then a significant percentage of children with a normal cystogram (that is, no VUR) but who have a damaged kidney on DMSA would be missed.

Postulated sequelae of renal scarring

The rationale for imaging children based on the belief that a damaged kidney secondary to a UTI leads on to hypertension is not proven. The only epidemiological study[1] showed a low risk of hypertension in patients with renal scarring (including those with severe or bilateral scarring) two decades after childhood UTI. It is noteworthy that all patients were followed up meticulously with prompt treatment of interval UTIs. There are two studies that do not support this view,[20 21] but neither represent epidemiological data, nor is the follow up as long as that of Wennerström and colleagues.[1] There is little evidence that renal scarring secondary to UTI leads to chronic renal failure, dialysis, or renal transplantation.[3 4] Wennerström and colleagues[3] state that overall glomerular filtration rate(GFR) did not decline after two decades in patients with unilateral scarring as the non-scarred kidney underwent compensatory hypertrophy. Although GFR did decline in patients with bilateral scarring, this did not reach statistical significance.

A stated aim of investigating UTI in the first year of life is to exclude congenital urinary tract abnormalities (such as posterior urethral valves) that may require surgery. However, as previously discussed, significant degrees of urethral obstruction are much more likely to be detected antenatally, or to present with clinical signs of renal impairment immediately after birth.

What is already known on this topic?

- Renal scarring following childhood urinary tract infection (UTI) may occur both in the presence and in the absence of vesico-ureteric reflux (VUR)
- Renal damage may be minimised or avoided following a first UTI, with careful clinical follow-up and prompt appropriate antibiotic treatment of subsequent UTIs
- The risks of hypertension and renal failure in later childhood and early adulthood in children with renal damage are now controversial
- At the present time, there is no clear international consensus about the imaging protocol to be followed following a first childhood UTI

What this study adds

- When urinary tract ultrasonography (US) is normal, there is no correlation between VUR demonstrated on cystography and renal scarring on DMSA (3–6 months after UTI)
- In UTI below the age of 1 year, when US is normal, DMSA should be the next imaging investigation
- Where US is normal, cystography is only indicated if DMSA is abnormal

Omission of cystography in at least some infants with UTI would be welcomed by both the parents of these children and many healthcare workers, in addition to reducing the considerable radiation burden to these babies. Bearing in mind that the link between renal scarring and long term sequelae is increasingly thought to be weak, and that with the widespread uptake of antenatal screening, less than 1% of US done at presentation with first UTI alters management,[10] another question could also be asked, ''Is any imaging necessary in the investigation of a first UTI in this age group?''. The benefit or lack of benefit of routine antibiotic prophylaxis will have to be shown before our last question can be answered.

Conclusion

Our results suggest that cystography contributes little to the management of UTI before the age of 1 year, in the context of a normal urinary tract ultrasound examination. In this context, a normal DMSA study reinforces the redundancy of cystography. We would be interested in the results of other investigators, studying similar populations, using similar inclusion criteria. Review of guidelines for the management of UTI in this age group, on both sides of the Atlantic, is timely.

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REFERENCES

1 **Wennerström M**, Hansson S, Hedner T, *et al*. Ambulatory blood pressure 16–26 years after the first urinary tract infection in childhood. *J Hypertens* 2000;**18**:485–91.
2 **Martinell J**, Jodal U, Lidin-Janson G. Pregnancies in women with and without renal scarring after urinary infections in childhood. *BMJ* 1990;**300**:840–4.
3 **Wennerström M**, Hansson S, Jodal U, *et al*. Renal function 16 to 26 years after the first urinary tract infection in childhood. *Arch Pediatr Adolesc Med* 2000;**154**:339–45.
4 **Craig JC**, Irwig LM, Knight JF, *et al*. Does treatment of vesicoureteric reflux in childhood prevent end-stage renal disease attributable to reflux nephropathy? *Pediatrics* 2000;**105**:1236–41.
5 **Downs SM**. Technical report: Urinary tract infections in febrile infants and young children. *Pediatrics* 1999;**103**:e54.
6 **Wheeler D**, Vimalachandra D, Hodson EM, *et al*. Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials. *Arch Dis Child* 2003;**88**:688–94.
7 **Gordon I**, Barkovics M, Pindoria S, *et al*. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalised with urinary tract infection: a systematic review and meta-analysis. *J Am Soc Nephrol* 2003;**14**:739–44.
8 **Royal College of Physicians**. *Guidelines for the management of acute urinary tract infection in childhood*. Report of a working group of the Research Unit. *JR Coll Physicians Lond* 1991;**25**:36–42.
9 **American Academy of Pediatrics Committee on Quality Improvement Subcommittee on Urinary Tract Infection**. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999;**103**:843–52.
10 **Hoberman A**, Charron M, Hickey RW, *et al*. Imaging studies after a first febrile urinary tract infection in young children. *N Engl J Med* 2003;**348**:195–202.
11 **Hitzel A**, Liard A, Vera P, *et al*. Color and power Doppler sonography versus DMSA scintigraphy in acute pyelonephritis and in prediction of renal scarring. *J Nucl Med* 2002;**43**:27–32.
12 **Kavanagh EC**, Ryan S, Awan A, *et al*. Can MRI replace DMSA in the detection of renal parenchymal defects in children with urinary tract infections? *Pediatr Radiol* 14 October 2004 (electronic only).
13 **Christian MT**, McColl JH, MacKenzie JR, *et al*. Risk assessment of renal cortical scarring with urinary tract infection by clinical features and ultrasonography. *Arch Dis Child* 2000;**82**:376–80.
14 **Patel K**, Charron M, Hoberman A, *et al*. Intra- and inter-observer variability in interpretation of DMSA scans using a set of standardised criteria. *Pediatr Radiol* 1993;**23**:506–9.
15 **Rossleigh MA**, Farnsworth RH, Leighton DM, *et al*. Technetium-99m dimercaptosuccinic acid scintigraphic studies of renal cortical scarring and renal length. *J Nucl Med* 1998;**39**:1280–5.
16 **Piepsz A**, Blaufox MD, Gordon I, *et al*. Consensus on renal cortical scintigraphy in children with urinary tract infection. *Semin Nucl Med* 1999;**29**:160–74.
17 **Jaeschke R**, Guyatt GH, Sackett DL. Users' guide to the medical literature: III. How to use an article about a diagnostic test: B, What are the results and will they help me in caring for my patients? *JAMA* 1994;**271**:703–7.
18 **Fischer JE**, Bachmann LM, Jaeschke R. A readers' guide to the interpretation of diagnostic test properties: clinical example sepsis. *Intensive Care Med* 2003;**29**:1043–51.
19 **Olbing H**, Smellie JM, Jodal U, *et al*. New renal scars in children with severe VUR: a 10-year study of randomised treatment. *Pediatr Nephrol* 2003;**18**:1128–31.
20 **Goonesekera CDA**, Shah V, Wade AM, *et al*. 15-year follow-up of renin and blood pressure in reflux nephropathy. *Lancet* 1996;**347**:640–3.
21 **Patzer L**, Seeman T, Luck C, *et al*. Day and night-time blood pressure elevation in children with higher grades of renal scarring. *J Pediatr* 2003;**142**:117–22.